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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/099,307	06/18/98	ERTL J	02481.1597

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EXAMINER	
SAOUD, C	
ART UNIT	**PAPER NUMBER**
1646	9

DATE MAILED: 08/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/099,307	ERTL et al.
Examiner	**Group Art Unit**
Christine Saoud	1646

☒ Responsive to communication(s) filed on *Jul 14, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-36, 41-58, and 60-67* is/are pending in the application.

Of the above, claim(s) *2-27, 29-36, 41-58, and 60-67* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. Applicant's amendment to claim 1 in paper #4 filed 18 June 1998 has been entered into the instant application. Applicant's amendment to claims 63-66 has been entered in paper #8, filed 14 July 1999.

Election/Restriction

2. Applicant's election with traverse of the species of SEQ ID NO:3 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the search of the subject matter of any one species would encompass a search for the subject matter of the remaining species. This is not persuasive because the MPEP indicates that an election of species should be required prior to a search on the merits "in all applications containing both species claims and generic or Markush claims" (see MPEP 808.01(a)). The fact that there are such a multiplicity of species that an unduly extensive and burdensome search is required (as indicated by the sheer number of embodiments which are encompassed by the generic claims), dictations that a requirement for an election of species should be made prior to a search of the generic claim. The species election provides that the generic claim will be examined, but the claims will be limited to the elected species if no generic claim is finally held to be allowable. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by

37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The requirement is still deemed proper and is therefore made FINAL.

3. Applicant indicates in paper #8 that the claims which read on the elected species are claims 1 and 28 (see response at page 2, last sentence of paragraph 2). Therefore, claims 2-27, 29-36, 41-58 and 60-67 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 8. Claims 1 and 28 are currently under examination.

Sequence Compliance

4. The specification does not comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. There are nucleotide sequences present at pages 18-22 of the specification which are not represented by a sequence identifier in the Sequence Listing. A new Sequence Listing in both computer readable form and paper copy are required which include all amino acid and nucleic acid sequences which are encompassed by 37 CFR 1.821 (see MPEP 2422). The entire specification should also be carefully reviewed for compliance, and a substitute specification may be required if the number of amendments that would need to be made are considerable (i.e. more than about 50). If a substitute specification is required, Applicant should

carefully review the M.P.E.P. for the procedures on filing such and possibly contact the Examiner in order to assure that the substitute specification is correctly prepared. Correction is required. See M.P.E.P. 2422.03.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

6. The instant specification contains a Figure in the body of the specification at page 26. Figures are not permitted in the body of the specification, but are to come after the Abstract of the Disclosure (see 37 CFR §1.77). Additionally, 37 CFR §1.74 indicates that "[w]hen there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures, and to the different parts by use of reference letters" (see MPEP 608.01(f)). Applicant should note that if the Figure at page 26 is to be viewed as multiple panels, the correct numbering would be to label them as Figures 1A-1F. If the Figure will not be referred to in this manner, it should be labeled as "Figure" and not "Figure 1". When there is a single figure, it does not receive a numeral.

Specification

7. The abstract of the disclosure is objected to because it is not limited to a single paragraph. Correction is required. See MPEP § 608.01(b).

8. The title of the invention is not descriptive. The recitation that the invention is "Novel" is not descriptive of what is being claimed, and the word "Novel" should not appear in the title. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brange (U.S. Pat. No. 5,597,796) in view of Markussen et al. (WO 92/00321) and Brange et al. (WO 89/10937).

Brange teaches insulin analogues having a negative charge at neutral pH and a reduced tendency to association (see abstract). This advantage is achieved by the substitution of an amino acid selected from the group consisting of Asp, Glu, Ser, Thr, His and Ile for a neutral or basic amino acid. The preferred amino acids for substitution are Asp and/or Glu (see column 7, lines 7-10) which result in a monomeric insulin analogue with a greater negative charge at neutral pH

than that of human insulin. The preferred amino acid positions for substitution are indicated as X, Y, Z and W in formula III found column 8. Brange specifically teaches that the substitution of the Lys at B29 into Glu or Asp will provide a 2 negative charge shift (see column 8 at lines 17-19) and claim 4 is specifically directed to an insulin analogue having a substitution at B29 with Asp or Glu. Brange does not teach this modification in combination with a substitution at B3.

Markussen et al. teach that "a positive charge in the N-terminal end of the B-chain gives rise to insulin analogues with a highly prolonged insulin action as compared to human insulin and also have a high in vivo potency" (see page 1, lines 26-29). Markussen specifically indicate that any one of amino acids B1 to B6 should be replaced by a basic amino acid residue; i.e. a lysine (Lys) or arginine (Arg).

Brange et al. teach the general concept of combining modifications at different amino acid positions in insulin in order to receive the combined benefit of the multiple modifications. For example, the passage at page 3, lines 26-32, describe the combination of two substitutions for the benefit of stability and protracted activity at acid pH.

Therefore, it would have been *prima facie* obvious at the time of the instant invention to make the insulin analogue of Brange wherein the amino acid at position B29 is substituted with Glu and combine the substitution of Lys for B3 as taught by Markussen et al. in order to obtain an insulin analogue which is stabilized against association and also has a prolonged insulin action. One would be motivated to combine these modifications for their expected benefit because these are both desirable properties of insulin and because Brange et al. teach that combination of

substitutions in insulin for different benefits is routinely accomplished. Therefore, the invention as a whole would have been *prima facie* obvious, absent evidence to the contrary.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 20, 1999

CHRISTINE SAOUD
PATENT EXAMINER
Christine Saoud

FILE COPY Application No. 09/099,307

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☑ 7. Other: See Office Action

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.